OBJECTIONS

(1) The Office Action objected to Figure 2 because the figure is described as "Table 1". Applicants provide a substitute Figure 2, which substitute Figure 2 is labeled "Figure 2", in place of "Table 1".

(2) The Office Action objected to claims 5 because of the recitation of "at201". Applicants respectfully point out that the designations "at201" and "ta201" do not refer to the same marker. This is shown in the specification on page 31, lines 1-12; and on page 28, line 16.

(3) The Office Action objected to claims 5 and 6 "because they appear to be duplicative claims". These claims are not duplicative, as explained in (2), above.

(4) The Office Action objected to claim 16 because it does not further limit claim 15. Applicants have amended claim 16 so that it further limits claim 15.

CLAIM REJECTIONS

Rejection Under 35 U.S.C. §112, second paragraph

Claims 2-7, 9-13, 15, and 16 were rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite.

Specifically, the Office Action stated that the claims are indefinite over the recitation of "inclusive" because as written the claims are unclear as to what this term refers to. Applicants respectfully traverse. The word "inclusive" is defined in a standard dictionary as "comprehending the stated limits or extremes." Thus, the meaning of this term is clear.

Nevertheless, in the interest of expediting prosecution, claims 2-4, 6, 7, 9-11, 13, 15, and 16 are amended to recite the phrase "between and inclusive of", as suggested in the Office Action.

The Examiner is thus respectfully requested to withdraw this rejection.

Rejection Under 35 U.S.C. §112, first paragraph

Claims 1-13, 15, and 16 were rejected under 35 U.S.C. §112, first paragraph on the basis that the specification allegedly does not provide enablement commensurate in scope with the claims.

Specifically, the Office Action stated that the specification does not provided enablement for a method of detecting a locus for bipolar mood disorder by detecting polymorphisms between and inclusive

of SAVA5 and ga203 or any of the other recited markers. The Office Action further stated that the specification has not provided sufficient guidance to allow the skilled artisan to detect a bipolar mood disorder susceptibility locus without undue experimentation. Applicants respectfully traverse.

The present invention provides, for the first time, a localization of a severe bipolar mood disorder (BP-I) susceptibility locus to a 300 to 500 kb region of the short arm of chromosome 18 (referred to herein as "the identified region"). The inventors demonstrated the feasibility of genome screening using linkage disequilibrium (LD) mapping using the recently available set of markers covering the genome. The inventors demonstrated that the identified region is linked to BP-I. The localization of a BP-I susceptibility locus to the 300-500 kb region is a major contribution. The inventors have narrowed the region within which the susceptibility locus is contained, from the entire genome to a narrow interval. The invention provides a convenient diagnostic tool for clinicians, who typically rely upon standard interview methods to make a diagnosis of BP. Rather than relying solely on subjective interview processes in diagnosing BP, clinicians can take advantage of the present invention to identify BP-susceptible individuals.

Discussion of cited publications

The Office Action cites a number of publications to support the contention that the specification is not enabling for the full scope of the claims. These publications include Stine (1995); McInnes (1996), Esterling (1997), Ewald (1997), Gershon (1998), and Nöthen (1999).

The Office Action states that "even as [of] 1999 no specific polymorphisms or loci have been identified as a bipolar susceptibility locus" (Office Action, page 4) and cited these publications as evidence of "the extensive amount of unpredictability in this field" (Office Action, page 6).

A careful analysis of each of the cited references reveals that none of these references supports a non-enablement rejection of the claims.

It should be noted that McInnes discloses much of the instant invention, and is the inventors' own work. The Office Action cited McInnes as teaching that "interpreting results from linkage analysis of bipolar mood disorder ... is very difficult". This statement is taken from the Background section of McInnes, which discusses some of the drawbacks to previous approaches for identifying loci associated with complex behavioral phenotypes, and goes on to provide an approach to address these drawbacks. Thus, the statements in McInnes cited in the Office Action as support for lack of enablement were merely

statements of the background problem. The present invention addresses these problems, and provides a solution.

The other publications do not focus on the region of 18p11.3, in which the region identified in the instant invention is localized. As a reference, a schematic representation of chromosome 18, showing the relative positions of several chromosome 18 markers, is provided as Exhibit 1, attached hereto. In Exhibit 1, approximate distances (from a Généthon map) between the centromere and the p11.3 and q23 regions are shown.

Upon careful reading of Stine, it is evident that Stine focused on a pericentromeric region of chromosome 18, as shown in Figure 2 of Stine. It is not seen how Esterling's disclosure can be interpreted to support a non-enablement rejection in the instant application, since, as the Office Action correctly noted, Esterling focused on the p11.2 region of chromosome 18. The p11.2 region is distant from the region identified in the instant application, which localizes to 18p11.3. Ewald and Gershon also focused on a region other than 18p11.3. Furthermore, Ewald and Gershon both purport to cite the problems in the art with respect to identifying loci associated with BP, yet neither of these references considers McInnes, and therefore neither considers the advancements to the field by McInnes, who discloses linkage of BP with the identified locus. Nöthen reports that 23 chromosome 18 markers were genotyped, and provide data relating to these markers in Table 1. However, as shown in Figure 1 of Nöthen, only two markers, i.e., PACAP and D18S62, localize to 18p11.3. All of the other markers localize to regions of chromosome 18 other than the region identified in the instant application. Thus, Nöthen also focused on a region other than 18p11.3.

Thus, rather than supporting a non-enablement rejection, the cited references merely point out the problems in the field, which the present inventors were able to surmount.

Nevertheless, and solely in the interest of expediting prosecution, claim 1 is amended to recite "A method of detecting the presence of a bipolar mood disorder susceptibility polymorphism". Support for this amendment is found throughout the specification, and in particular on page 24, lines 24-27.

Applicants add new claims 17 to 24, which are drawn to subject matter which the Office Action indicated is enabled. Office Action, page 3. Support for new claims 17-24 is found throughout the specification, e.g., at page 28, lines 12-20.

Applicants submit that the rejection of claims 1-13, 15, and 16 under 35 U.S.C. §112, first paragraph have been adequately addressed in view of the arguments presented above. The Examiner is thus respectfully requested to withdraw this rejection and allow the claims.

Rejection Under 35 U.S.C. §102 (b)

Claims 15 and 16 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Stine et al. ((1995) *Am. J. Hum. Genet.* 57:1384-1394; hereinafter "Stine").

Specifically, the Office Action stated that Stine teaches "an isolated polynucleotide which is marker D18S59 which they showed was linked to bipolar mood disorder". Office Action, page 7. The Office Action concluded that Stine teaches the claimed isolated polynucleotides because the D18S59 marker is located within the 500 kb region between SAVA5 and ga203. Applicants respectfully traverse.

Stine is not available as a 35 U.S.C. §102(b) reference. The present application claims benefit of priority to provisional application serial no. 60/023,438, filed August 23, 1996. Stine was published in December, 1995, less than one year before the August 23, 1996 priority date. Accordingly, Stine is not §102(b) art against the instant application.

Nevertheless, the disclosure of Stine does not anticipate the invention recited in claims 15 and 16. Stine does not teach that D18S59 is linked to bipolar mood disorder. Rather, Stine reports a linkage of BP to a pericentromeric region of chromosome 18 (summarized in Stine, Figure 2, page 1391; see also the schematic representation of chromosome 18 in Exhibit 1). Stine notes that the LOD scores for loci on 18p, including D18S59, were "uniformly negative" (Stine, page 1388, column 2, first incomplete paragraph). As noted in the instant specification, in contradistinction to Stine's reported findings, the inventors "did not show any evidence for association of BP-I with any pericentromeric markers" (specification, page 25, lines 6-10). Thus, while Stine focused on a pericentromeric region, the instant invention relates to a narrow, telomeric interval.

Furthermore, as noted in the Office Action, Stine does not teach an isolated 500 kb region between and inclusive of SAVA5 and ga203, and furthermore did not teach that this region is linked to BP. Accordingly, Stine does not anticipate the instant invention.

The Examiner is thus respectfully requested to withdraw this rejection.

III. CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested. If the Examiner finds that a Telephone Conference would expedite the prosecution of this application, she is invited to telephone the undersigned at the number provided.

No fee is believed due with this amendment. However, the Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extension of time, or credit any overpayment to Deposit Account No. 50-0815, order number 6510/142CON.

Respectfully submitted,

Date: Oct. 25, 1999

By: _____
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Enclosure: Exhibit 1
Substitute Figure 2

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